P1-02-10

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Real-world analysis of interstitial lung disease/pneumonitis in patients with HER2-positive unresectable or recurrent breast cancer treated with trastuzumab deruxtecan: all-patient post-marketing surveillance study in Japan

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Objectives

- To investigate the incidence of ILD/p and factors associated with the development of ILD/p among breast cancer patients treated with T-DXd in the real-world setting in Japan.

Conclusions

- The incidence of adjudicated drug-related ILD was: [Any Grade: 16.06%; Grade ≥3: 3.00%; Grade 5: 0.98%] which was not notably different from that in clinical studies, suggesting no new safety concerns were identified in this PMS, despite the fact that these were real-world patients with higher ECOG performance status and more comorbidities than those in clinical studies.
- Clinical factors of interest for the development of adjudicated drug-related ILD may include male gender, higher BMI, medical history and/or comorbidity of ILD, and renal impairment. Further investigation is warranted to confirm risk factors for ILD/p.

Limitations

- This study was non-blinded, non-randomized, and there was no control arm (all of which can lead to inherent risks for bias).
- One of the identified factors of interest (male gender) had a small sample size (n=8); this can reduce the validity of this finding.
- This study was conducted in Japan; the study findings must be interpreted with caution when generalizing to other populations outside of Japan.

Abbreviation

ILD, interstitial lung disease; ILD/p, ILD/pneumonitis; T-DXd, trastuzumab deruxtecan; PMS, post-marketing surveillance; BMI, body mass index; GPSP, Good Post-marketing Study Practice; ORR, objective response rate; BOR, best objective response; ECOG, European Clinical Oncology Group; CLCr, creatinine clearance calculated using the Cockcroft-Gault equation; SpO_2, saturation of percutaneous oxygen; COPD, chronic obstructive pulmonary disease; CTCAE, Common Terminology Criteria for Adverse Events; CR, complete response; PR, partial response; SD, stable disease; PD, progression disease; NE, not evaluable; NA, not applicable

Introduction

- T-DXd has been approved for the treatment of HER2-positive unresectable or recurrent breast cancer after prior chemotherapy in Japan.
- While there is accumulating evidence demonstrating the effectiveness of T-DXd in various types of cancers, ILD/p are recognized as important identified risks associated with the use of T-DXd.
- Understanding the risk of ILD/p is crucial for optimizing ILD risk management and promoting the safe use of T-DXd.
- In this PMS, we investigate the incidence of ILD/p and factors associated with its development in the real-world setting in Japan.

Methods

- This PMS (jRCT1080225197) is a multicenter, observational study with an observation period of 18-months that enrolled all patients treated with T-DXd for breast cancer in Japan in accordance with the GPSP.
- All patients who initiated T-DXd treatment between May 25, 2020 (the day of launch) and November 30, 2021 were enrolled.
- Physician-assessed ILD/p events were retrospectively reviewed by an independent adjudication committee; events adjudicated as drug-related ILD were summarized.
- The factors associated with the development of adjudicated drug-related ILD were investigated using a Cox proportional hazards model.
- The effectiveness endpoints were ORR and intracranial ORR.

Reference

1) Powell CA, et al.: *ESMO Open* 7: 100554, 2022

Disclosure

This study was sponsored by Daiichi Sankyo Co., Ltd. In March 2019, AstraZeneca entered into a global development and commercialization collaboration agreement with Daiichi Sankyo for trastuzumab deruxtecan (T-DXd; DS-8201).

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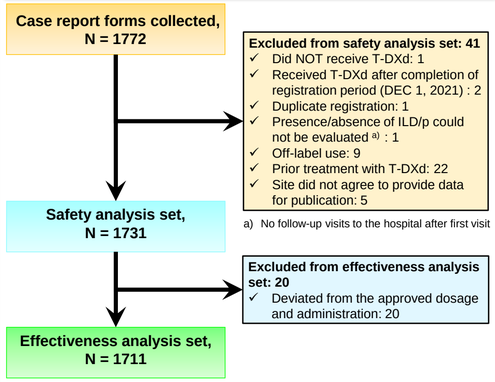
Results

1. Patient disposition



a) No follow-up visits to the hospital after first visit

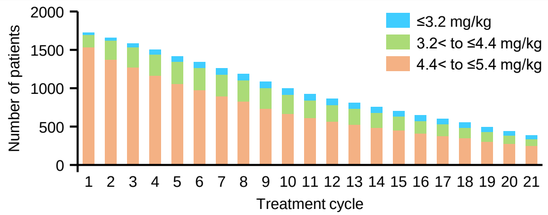
2. Patient demographics and clinical characteristics at baseline (safety analysis set)

	N = 1731, n (%)
Gender	
Male/Female	8 (0.5) / 1723 (99.5)
Age (years)	
Median (range)	60.0 (27–87)
≥65 years	637 (36.8)
ECOG performance status	
0-1 / 2-4	1594 (92.1) / 137 (7.9)
Site(s) of metastasis or recurrence*	
None	3 (0.2)
Local or lymph node / Lung or pleural	1055 (60.9) / 894 (51.6)
Bone / Liver	744 (43.0) / 609 (35.2)
Brain	367 (21.2)
Meninges or spinal fluid / Other	14 (0.8) / 212 (12.2)
Renal function (CLCr [mL/min])	
Normal: ≥90	605 (35.0)
Mild impairment: 60≤ to <90	767 (44.3)
Moderate impairment to end stage: <60	332 (19.2)
Unknown/missing	27 (1.6)

	N = 1731, n (%)
History of smoking	
Never / Past / Current / Unknown-missing	1257 (72.6) / 195 (11.3) / 34 (2.0) / 245 (14.2)
SpO_2 (%)	
<95 / ≥95 / Not implemented / Unknow or missing	51 (2.9) / 1297 (74.9) / 369 (21.3) / 14 (0.8)
Prior cancer therapy (regimens)	
≥2 / ≥3 / ≥6 / ≥10	1630 (94.2) / 1212 (70.0) / 426 (24.6) / 95 (5.5)
Medical history / comorbidity	
Respiratory disease	104 (6.0) / 87 (5.0)
ILD	24 (1.4) / 11 (0.6)
Radiation pneumonitis	40 (2.3) / 31 (1.8)
COPD or emphysema	1 (0.1) / 4 (0.2)
Asthma	29 (1.7) / 23 (1.3)
Other respiratory disease	15 (0.9) / 22 (1.3)
History of lung surgery	76 (4.4) / NA
Pleural effusion	NA / 230 (13.3)
Malignant tumors other than breast cancer	58 (3.4) / 26 (1.5)

* Including metastases or recurrence in multiple locations

3. Dosage change by treatment cycle (safety analysis set)



- **A certain number of patients had reduced dosage from the initial administration.**
- **No cases of dosing above the approved dosage (5.4 mg/kg) were observed.**

4. T-DXd treatment status at 18-months after treatment initiation

Treatment status at 18-months	N = 1731, n (%)
Ongoing	434 (25.1)
Discontinued	1297 (74.9)
Reason for treatment discontinuation*	
Progression of primary disease (including death)	797 (46.0)
Adverse events (other than ILD/p)	98 (5.7)
ILD/p (reported by treating physician)	280 (16.2)
Lost to follow up	21 (1.2)
Refusal or request of the patient	89 (5.1)
Other	58 (3.4)

Data are n (%), * These categories are not mutually exclusive

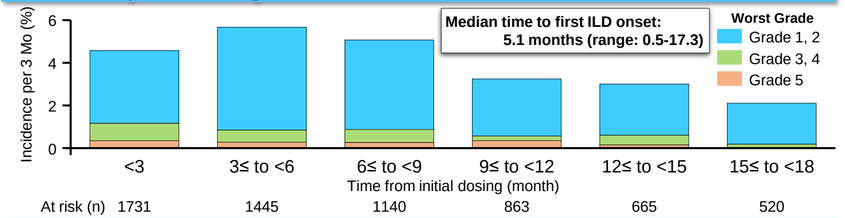
- **At 18-months after treatment initiation, 25.1% of patients continued treatment with T-DXd.**
- **The most common reason for treatment discontinuation was disease progression, including death.**

5. Incidence of adjudicated drug-related ILD

N	Worst CTCAE Grade, n (%)						
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any Grade	Grade ≥3
1731	125 (7.22)	101 (5.83)	34 (1.96)	1 (0.06)	17 (0.98)	278 (16.06)	52 (3.00)

[Safety analysis set] Median duration of T-DXd treatment: 9.40 months (range: 0.7-17.9)

6. Time to adjudicated drug-related ILD incidence



Adjudicated drug-related ILD was observed throughout the 18-month observation period.

7. Outcome of adjudicated drug-related ILD (by worst Grade)

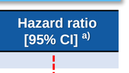
Worst Grade	N	Outcome (up to 6 months of follow-up after onset of ILD), n (%)					
		Resolved	Resolving	Resolved with sequelae	Not resolved	Fatal	Unknown/ missing
Any Grade	278	146 (52.52)	69 (24.82)	15 (5.40)	26 (9.35)	17 (6.12)	5 (1.80)
Grade 1	125	78 (62.40)	28 (22.40)	0 (0)	15 (12.00)	0 (0)	4 (3.20)
Grade 2	101	60 (59.41)	29 (28.71)	5 (4.95)	6 (5.94)	0 (0)	1 (0.99)
Grade 3	34	8 (23.53)	12 (35.29)	9 (26.47)	5 (14.71)	0 (0)	0 (0)
Grade 4	1	0 (0)	0 (0)	1 (100)	0 (0)	0 (0)	0 (0)
Grade 5	17	0 (0)	0 (0)	0 (0)	0 (0)	17 (100)	0 (0)
Grade ≥3	52	8 (15.38)	12 (23.08)	10 (19.23)	5 (9.62)	17 (32.69)	0 (0)

The CTCAE grades of adjudicated drug-related ILD at the onset for the 17 patients with a fatal outcome were as follows: Grade 1 for 3 patients, Grade 2 for 3 patients, and Grade 3 for 11 patients.

More than 80% of ILD had resolved, were resolving, or resolved with sequelae within 24 weeks from the onset, while the proportion decreases to less than 60% in the cases of Grade ≥3.

8. Factors of interest for the development of adjudicated drug-related ILD

Variables	Patients N = 1730	ILD case N = 277	Hazard ratio [95% CI] a)
Gender			
Female (reference)	1722	273	-
Male	8	**4**	**3.634 [1.299, 10.163]**
BMI (kg/m^2)			
<21.3 (Median) (reference)	858	118	-
≥21.3 (Median)	857	**157**	**1.649 [1.275, 2.133]**
Unknown/missing	15	2	1.987 [0.465, 8.499]
ILD (medical history and/or comorbidity)			
No (reference)	1697	266	-
Yes b)	33	**11**	**2.237 [1.210, 4.134]**
Renal function (CLCr [mL/min])			
Normal: ≥90 (reference)	605	77	-
Mild impairment: 60≤ to <90	766	**140**	**1.719 [1.272, 2.322]**
Moderate impairment to End stage: <60 b)	332	**58**	**1.850 [1.240, 2.761]**
Unknown/missing	27	2	0.648 [0.149, 2.819]



a) Calculated using a multivariate Cox proportional hazards model
b) "Potential risk factor of interest" for ILD/p identified in the published literature (Powell et al., 2022)

Baseline factors included in the model were gender, ECOG-PS, serum albumin levels, SpO_2, age, body weight, BMI, history of smoking, time since the diagnosis of recurrent/unresectable breast cancer, the stage of unresectable/recurrent breast cancer, hormone receptor expression status, HER2 receptor expression status, lung or pleura metastasis or recurrence, liver metastasis or recurrence, brain metastasis or recurrence, prior cancer therapy for unresectable or recurrent breast cancer, the number of regimens for all prior treatments against breast cancer, prior chest radiation therapy, and other medical history and/or comorbidity (ILD, radiation pneumonitis, COPD, emphysema, asthma, pleural effusion, and history of lung surgery), renal function, and hepatic function.

9. Effectiveness

Effectiveness in the effectiveness analysis set

N	ORR (CR + PR)		BOR a), n (%)				
	n (%)	95% CI	CR	PR	SD	PD	NE
1711	1036 (60.5)	58.2, 62.9	98 (5.7)	938 (54.8)	448 (26.2)	155 (9.1)	72 (4.2)

Effectiveness among patients with brain metastasis

N	Intracranial ORR (CR + PR)		Intracranial BOR a), n (%)				
	n (%)	95% CI	CR	PR	SD	PD	NE
365	133 (36.4)	31.5, 41.4	31 (8.5)	102 (27.9)	135 (37.0)	20 (5.5)	74 (20.3)

a) The best objective response was evaluated by the investigators according to the "RECIST Guidelines ver. 1.1"

[Effectiveness analysis set] Median duration of T-DXd treatment: 9.23 months (range: 0.7-17.9)